

Romiplostim (Nplate), a Treatment Option for Immune (Idiopathic) Thrombocytopenic Purpura

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INTRODUCTION¹⁻⁴

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune bleeding disorder caused by an abnormally low level of platelets. In patients with ITP, antibodies against platelets are produced. The antibodies coat the platelets, causing them to be vulnerable to immediate uptake and destruction by macrophages within the spleen.

Typically, symptoms of ITP develop when platelet counts drop below $50 \times 10^9/L$. Petechiae, epistaxis, and gingival bleeding can occur. Patients may also report easy bruising and bleeding from minor wounds. Serious bleeding, including overt gastrointestinal (GI) bleeding, gross hematuria, and intracranial hemorrhage may occur; however, these events are considered infrequent. Nevertheless, serious bleeding sometimes occurs in elderly patients, and this can be significant. Bleeding can be attributed to other comorbidities and possible precipitating factors that can potentiate a bleeding episode.

ETIOLOGY AND DIAGNOSIS

The onset of thrombocytopenia symptoms is usually insidious, and spontaneous remission of symptoms is often

uncommon. The emergence of ITP can be acute or chronic, with each etiologic factor having distinctive differences. Acute ITP classically affects children from 2 to 10 years of age, and a complete recovery may be experienced within six months, usually without treatment. Acute cases may last for up to six months.

Chronic ITP usually affects adults. Treatment is essential for these patients because the condition rarely resolves independently and there is a potential for serious consequences. Chronic ITP tends to persist for an extended period of time, usually more than six months.

The diagnosis is made through one of exclusion because there are many other possible causes of thrombocytopenia. A complete patient evaluation, including a medication history, a physical examination, a complete blood count (CBC), and a peripheral blood smear, is a vital tool needed to support the diagnosis of ITP. Other conditions associated with thrombocytopenia should take precedence when patients are thought to have ITP. Table 1 presents some possible causes of thrombocytopenia.

Therapies for chronic ITP can include agents such as corticosteroids, azathioprine, cyclophosphamide, rituximab (Rituxan, Genentech), cyclosporine, intravenous (IV) immunoglobulin, vinca alkaloids, and danazol, as well as surgical intervention such as splenectomy. A more recent addition to the armamentarium is romiplostim for subcutaneous (SQ) injection (Nplate, Amgen), a thrombopoietin (TPO) receptor.

INDICATION AND USAGE⁵⁻⁷

The FDA approved romiplostim on August 22, 2008, for the treatment of

chronic ITP in patients who have had an unfavorable response to corticosteroids, immunoglobulins, or splenectomy. Romiplostim is recommended in patients whose degree of thrombocytopenia increases the risk of bleeding. It is not recommended for normalizing the platelet count.

CLINICAL PHARMACOLOGY^{5,7,8}

Romiplostim is an Fc-peptide fusion protein (peptibody) that stimulates intracellular transcriptional pathways, which results in increased platelet production by binding to the TPO receptor. Produced by recombinant DNA technology

Table 1 Possible Causes of Thrombocytopenia*

Pregnancy

- Pre-eclampsia
- Gestational thrombocytopenia

Drug-Induced

- Quinine
- Quinidine
- Sulfonamides
- Gold compounds
- Heparin
- Glycoprotein IIb/IIIa inhibitors
- Antibiotics (i.e., beta-lactams, vancomycin)
- Antiepileptic agents (i.e., valproic acid, phenytoin)

Infection

- HIV
- Hepatitis
- Mononucleosis

Congenital

- Von Willebrand disease
- Fanconi syndrome

*Numerous agents and other congenital conditions can cause thrombocytopenia; this table is not entirely inclusive.

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in *Escherichia coli*, romiplostim mimics human TPO. When binding occurs to the TPO receptors, it promotes the growth of bone marrow megakaryocyte colony-forming cells, leading to increased platelet production via JAK2 and STAT5 kinase pathways. This mechanism of action is illustrated in Figure 1.

PHARMACOKINETICS AND PHARMACODYNAMICS⁵

After a single SQ injection with romiplostim (dose range, 1–10 mcg/kg) in patients with chronic ITP, the onset of peak response was reported to be 1.3 to 14.9 times greater than baseline platelet values over two to three weeks. In clinical trials, romiplostim demonstrated dose-dependent increases in platelet counts after treatment was discontinued. The time to peak concentration (T_{max}) with romiplostim is approximately 7 to 50 hours (median, 14 hours for the post-weekly dose).

The elimination of romiplostim occurs according to the TPO receptor located on the platelet. It is interesting that the drug's serum concentration is inversely related to the patient's platelet count. Thus, a patient with a relatively low platelet count typically has higher serum concentrations of romiplostim, and vice versa. The drug's half-life ranges from 1 to 34 days (median, 3.5 days).

CLINICAL TRIALS^{6,8,9}

Clinical data on the safety and efficacy of romiplostim are available from two parallel phase 3 studies. These randomized, double-blind, placebo-controlled, multicenter studies evaluated romiplostim for the treatment of ITP in splenectomized or non-splenectomized patients with chronic ITP.

One study enrolled patients who had undergone splenectomy; the other trial enrolled patients who had not. The studies evaluated 125 patients with chronic ITP not receiving ITP therapy (except those receiving stable corticosteroid doses, azathioprine, or danazol, or both) and who completed at least one prior therapy with baseline platelet counts of $30 \times 10^9/L$ or below. Patients were assigned, in a 2:1 ratio, to receive SQ romiplostim 1 mcg/kg every week for 24 weeks or placebo. In the romiplostim group, 42 patients had undergone splenectomy and 41 patients had not. In

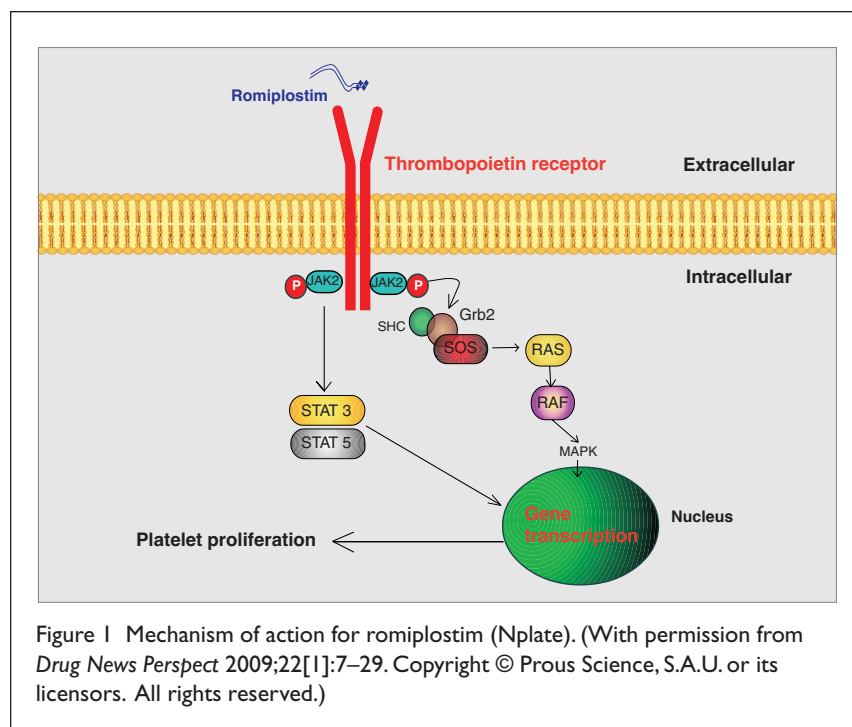


Figure 1 Mechanism of action for romiplostim (Nplate). (With permission from Drug News Perspect 2009;22[1]:7–29. Copyright © Prous Science, S.A.U. or its licensors. All rights reserved.)

the placebo group, 21 patients had undergone splenectomy and 21 had not. The doses were adjusted in order to maintain platelet counts of $50 \times 10^9/L$ to $200 \times 10^9/L$ during weeks 2 through 24. The patients entered a follow-up period from weeks 25 to 36.

The primary endpoints of the studies were the incidence of a durable platelet response (a platelet count of $50 \times 10^9/L$ or higher) for at least six of the final eight weeks of the treatment period. Other endpoints included overall response, the number of weeks with a platelet count response of $50 \times 10^9/L$ or more, discontinuation or reduction of concurrent ITP medications, the use of a rescue medication, and safety. The median baseline platelet count was $15 \times 10^9/L$ in the placebo patients and $14 \times 10^9/L$ in the romiplostim patients. Durable platelet response was achieved by 16 of 42 splenectomized romiplostim patients and by none of the 21 placebo patients; the difference in the proportion of patients responding was 38% (confidence interval [CI], 23.4–52.8; $P = 0.0013$).

In the non-splenectomized group, 25 of the 41 romiplostim patients and one of the 21 placebo patients had a durable response; the difference in the proportion of splenectomized patients responding was 56%; (CI, 38.7–73.7; $P < 0.0001$).

The overall platelet response was achieved by 88% of the non-splenectomized patients and by 79% of the splenectomized patients in the romiplostim group, compared with 14% of the non-splenectomized and none of the splenectomized patients in the placebo group ($P < 0.0001$). In the romiplostim group, 87% of patients reduced or discontinued concurrent therapy, compared with 38% of those receiving placebo.

Adverse events were similar between the romiplostim and placebo groups, but romiplostim's safety could not be completely assessed because of the small study population. In these two trials, romiplostim was well tolerated and effective in patients with ITP.

ADVERSE DRUG REACTIONS⁵

Data on adverse drug events (AEs) were compiled from two parallel phase 3 studies and an open-label, single-arm study in which patients received romiplostim over an extended period. The most commonly reported AE in all of the clinical trials was mild-to-moderate headache in 35% of patients receiving romiplostim and in 32% of patients receiving placebo (Table 2). Serious AEs included bleeding, myelofibrosis, antibody formation, popliteal artery thrombosis, increased bone marrow reticulin,

Table 2 Adverse Drug Reactions Identified with the Use of Romiplostim (Nplate) In Two Placebo-Controlled Studies

Preferred Term	Nplate (n = 84)	Placebo (n = 41)
Arthralgia	26%	20%
Dizziness	17%	0%
Insomnia	16%	7%
Myalgia	14%	2%
Pain in extremity	13%	5%
Abdominal pain	11%	0%
Shoulder pain	8%	0%
Dyspepsia	7%	0%
Paresthesia	6%	0%

From Nplate prescribing information, 2008.⁵

and thrombocytopenia upon discontinuation of therapy.

PREGNANCY⁵

No well-controlled trials of romiplostim use have been conducted in pregnant women. Romiplostim is therefore classified as a Pregnancy Category C drug.

DRUG INTERACTIONS⁵

No significant drug interactions have been documented with the use of romiplostim; ongoing trials are needed in this area. Consequently, careful evaluation of

agents that cause changes in platelet counts may ultimately affect the efficacy of romiplostim.

CONTRAINDICATIONS⁵

The manufacturer has not listed any contraindications.

PRECAUTIONS AND WARNINGS⁵

Romiplostim use can increase the risk of the development or progression of reticulin fiber deposition within the bone marrow. In clinical studies, four of 271 patients stopped therapy because of this AE when doses above 5 mcg/kg were used.

Upon discontinuation of romiplostim, it is possible that more severe thrombocytopenia may result, which can increase the risk of significant bleeding. Monitoring the patient for bleeding is essential. In clinical trials, stopping romiplostim temporarily worsened thrombocytopenia, which typically resolved within 14 days after cessation of therapy. When romiplostim is discontinued, weekly CBC counts as well as platelet counts should be obtained for at least two weeks.

Romiplostim therapy has the potential to lead to thrombotic and thromboembolic complications as excessive increases in platelet counts become apparent. In controlled clinical trials, these events were similar between romiplostim and placebo. In efforts to reduce the risk of these serious complications, romi-

plostim is not indicated for restoring platelet counts to normal.

If the patient cannot maintain a platelet response with romiplostim, it is crucial to identify a cause of the hyporesponsiveness, such as neutralizing antibodies to the drug or bone marrow fibrosis. If the platelet count does not increase to a level that is sufficient to avoid clinically important bleeding at the highest weekly dose of 10 mcg/kg, romiplostim should be discontinued.

Patients receiving romiplostim tend to have an increased risk of hematological malignancies. In view of the warnings and precautions with its use, romiplostim is not indicated for treating thrombocytopenia resulting from any other cause except chronic ITP.

This agent is not intended for patients younger than 18 years of age.

DOSAGE AND ADMINISTRATION^{5,8}

The initial starting dose of romiplostim is 1 mcg/kg based on actual body weight (Table 3). The weekly dose should then be adjusted by increments of 1 mcg/kg until the platelet count is $50 \times 10^9/L$ or higher. The maximum weekly dose is 10 mcg/kg.

When platelet counts are greater than $200 \times 10^9/L$ for two consecutive weeks, the dose should be reduced by 1 mcg/kg weekly. When platelet counts exceed $400 \times 10^9/L$, the dose should be withheld until the count has fallen below $200 \times 10^9/L$. The dose can then be resumed with a reduction of 1 mcg/kg weekly.

Data on specific dose adjustments in patients with renal or hepatic impairment are limited, and dose adjustments are therefore not available from the manufacturer. Caution should be used when romiplostim is administered to these patients.

Romiplostim is supplied as a preservative-free, white lyophilized powder in 250- or 500-mcg vials for single use. The vial should be stored in the refrigerator and protected from light until reconstitution is warranted. The product is reconstituted with preservative-free Sterile Water for Injection using aseptic technique (Table 4). The vial should be gently swirled and should not be vigorously shaken. Romiplostim dissolves in approximately two minutes, and the contents of the solution should appear clear and colorless without any particulate matter or

Table 3 Dose Adjustments for Romiplostim (Nplate)

Platelet Count	Dose
Start	• 1 mcg/kg of actual body weight
Adjust • $<50 \times 10^9/L$	• Adjust weekly dose by increments of 1 mcg/kg unit until platelet count reaches $50 \times 10^9/L$ or greater. Do not exceed maximum weekly dose of 10 mcg/kg.
• $>200 \times 10^9/L$ for two consecutive weeks	• Reduce dose by 1 mcg/kg.
Discontinue • $>400 \times 10^9/L$	• Do not administer. Continue to assess platelet count weekly. When platelet count has fallen below $200 \times 10^9/L$, resume once-weekly dose, reduced by 1 mcg/kg.

Table 4 Reconstitution of Romiplostim (Nplate)

Nplate Single-Use Vial	Total Vial Content of Romiplostim		Sterile Water for Injection (Preservative-Free)		Deliverable Product and Volume	Final Concentration
250 mcg	375 mcg	Add	0.72 mL	=	250 mcg in 0.5 mL	500 mcg/mL
500 mcg	625 mcg	Add	1.2 mL	=	500 mcg in 1 mL	500 mcg/mL
From Nplate prescribing information, 2008. ⁵						

discoloration.

After reconstitution, romiplostim can be kept at room temperature or refrigerated for up to 24 hours before it is administered. It is injected subcutaneously, and special attention should be paid to the volume administered. Because the administration volume may be diminutive, an appropriate syringe should be used with gradations to 0.01 mL.

COST¹⁰

The average wholesale price (AWP) for each 250-mg single-use vial is \$1,275. The AWP of the 500-mcg single-use vial is \$2,550.

DISTRIBUTION

Romiplostim is available exclusively through the Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program. Only patients and health care professionals who are registered with this restricted distribution program are eligible to receive this agent. The program provides complete educational materials on the proper use of romiplostim. To enroll, health care practitioners can call 877-NPLATE (877-675-2831).

Prescribers and patients are required to understand the risk and benefits of treatment, and all patients should be given a medication guide. Prescribers must report any serious AEs to the Nplate phone number or to the FDA's MedWatch Program.

TRENDS IN THERAPY¹¹

Another new option for patients with ITP is eltrombopag, a nonpeptide TPO receptor agonist that can be given once daily orally on an empty stomach. Eltrombopag inhibits the organic anion transporting polypeptide OATP1B1,

which can increase the levels of drugs that are substrates for this enzyme. Eltrombopag is distributed through a restricted distribution program similar to that for romiplostim. The prescribing information carries a black-box warning for hepato-toxicity, and unlike the package insert for romiplostim, the literature for eltrombopag warns of cataracts.

CONCLUSION^{5,8,11}

Romiplostim (Nplate) is a TPO receptor agonist indicated for the treatment of chronic ITP. Patients receiving romiplostim should undergo a CBC count, a platelet count, and a peripheral blood smear, with monitoring of these values at the initiation of therapy. Monitoring should continue throughout treatment and after discontinuation of therapy. Follow-up laboratory assessment should be performed weekly, especially during the dose-adjustment phases, as well as monthly following an established stable dose. Laboratory assessments should be performed for at least two weeks after the patient stops therapy.

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